PCT/GB99/03366 WO 00/21948

Claims

A compound of formula (I) or a pharmaceutically acceptable derivative thereof: 1.

(I)

wherein:

5

25

30

one of Z¹, Z², Z³, Z⁴ and Z⁵ is N and the remainder are CH;

 R^1 is hydrogen, hydroxy; (C_{1-6}) alkoxy optionally substituted by (C_{1-6}) alkoxy, amino, 10 piperidyl, guanidino or amidino optionally N-substituted by one or two (C_{1-6}) alkyl, acyl or (C_{1-6}) alkylsulphonyl groups, NH₂CO, hydroxy, thiol, (C_{1-6}) alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C1-6) alkylsulphonyloxy; (C_{1-6}) alkoxy-substituted (C_{1-6}) alkyl; halogen; (C_{1-6}) alkyl; (C_{1-6}) 6) alkylthio; nitro; trifluoromethyl; azido; acyl; acyloxy; acylthio; (C₁₋₆) alkylsulphonyl; 15 (C₁₋₆)alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C1-6)alkyl, acyl or (C1-6)alkylsulphonyl groups;

either R² is hydrogen; and 20 R³ is in the 2- or 3-position and is hydrogen or (C₁₋₆)alkyl or (C₂₋₆)alkenyl optionally substituted with 1 to 3 groups selected from:

thiol; halogen; (C_{1-6}) alkylthio; trifluoromethyl; azido; (C_{1-6}) alkoxycarbonyl; (C_{1-6}) alkylcarbonyl; (C_{2-6}) alkenyloxycarbonyl; (C_{2-6}) alkenylcarbonyl; hydroxy optionally substituted by (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{1-6}) alkoxycarbonyl, (C_{1-6}) alkyl, (C_{1-6}) $_{6}$)alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C1-6)alkyl, (C2-6)alkenyl, (C1-6)alkylcarbonyl or (C2-6)alkenylcarbonyl; amino optionally mono- or disubstituted by (C_{1-6}) alkoxycarbonyl, (C_{1-6}) alkylcarbonyl, (C_{2-6}) alkenyloxycarbonyl, (C_{2-6}) 6)alkenylcarbonyl, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl, (C₂₋

6)alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6}) alkyl or (C_{2-6}) alkenyl; aminocarbonyl wherein the amino group is optionally mono- or disubstituted by (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{1-6}) alkoxycarbonyl,

 (C_{1-6}) alkylcarbonyl, (C_{2-6}) alkenyloxycarbonyl or (C_{2-6}) alkenylcarbonyl]; oxo; (C_{1-6}) 6) alkylsulphonyl; (C_{2-6}) alkenylsulphonyl; or (C_{1-6}) aminosulphonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl; or

- R^3 is in the 3-position and R^2 and R^3 together are a divalent residue = $CR^{5^1}R^{6^1}$ where R⁵¹ and R⁶¹ are independently selected from H, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, aryl(C₁₋₆) 6) alkyl and aryl(C2-6) alkenyl, any alkyl or alkenyl moiety being optionally substituted by 1 to 3 groups selected from those listed above for substituents on R³;
- R⁴ is a group -CH₂-R⁵ in which R⁵ is selected from: 10

 (C_{3-12}) alkyl; hydroxy (C_{3-12}) alkyl; (C_{1-12}) alkoxy (C_{3-12}) alkyl; (C_{1-12}) alkoxy $_{12}) alkanoyloxy (C_{3-12}) alkyl; (C_{3-6}) cycloalkyl (C_{3-12}) alkyl; hydroxy-, (C_{1-12}) alkoxy- or a superior of the control of th$ $(C_{1-12}) alkanoyloxy - (C_{3-6}) cycloalkyl (C_{3-12}) alkyl; \ cyano (C_{3-12}) alkyl; \ (C_{2-12}) alkenyl;$ (C₂₋₁₂)alkynyl; tetrahydrofuryl; mono- or di-(C₁₋₁₂)alkylamino(C₃₋₁₂)alkyl;

- $acylamino(C_{3-12})alkyl; (C_{1-12})alkyl- \ or \ acyl-aminocarbonyl (C_{3-12})alkyl; \ mono- \ or \ discovered acylamino (C_{3-12})alky$ 15 (C_{1-12}) alkylamino(hydroxy) (C_{3-12}) alkyl; optionally substituted phenyl (C_{1-2}) alkyl, $phenoxy(C_{1-2}) alkyl \ or \ phenyl(hydroxy)(C_{1-2}) alkyl; \ optionally \ substituted \ diphenyl(C_{1-2}) alkyl \ optionally \$ 2) alkyl; optionally substituted phenyl(C2-3) alkenyl; optionally substituted benzoyl or benzoylmethyl; optionally substituted heteroaryl(C1-2)alkyl; and optionally substituted
- 20 heteroaroyl or heteroaroylmethyl;

n is 0, 1 or 2;

A is NR^{11} , O, $S(O)_X$ or CR^6R^7 and B is NR^{11} , O, $S(O)_X$ or CR^8R^9 where x is 0, 1 or 2

and wherein: 25

- each of R⁶ and R⁷ R⁸ and R⁹ is independently selected from: H; thiol; (C₁₋₆)alkylthio; halo; trifluoromethyl; azido; (C_{1-6}) alkyl; (C_{2-6}) alkenyl; (C_{1-6}) alkoxycarbonyl; (C_{1-6}) alkoxycarbonyl; (C_{1-6}) alkoxycarbonyl; 6) alkylcarbonyl; (C_{2-6}) alkenyloxycarbonyl; (C_{2-6}) alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R3; (C1-
- 6)alkylsulphonyl; (C2-6)alkenylsulphonyl; or (C1-6)aminosulphonyl wherein the amino 30 group is optionally substituted by (C_{1-6}) alkyl or (C_{1-6}) alkenyl; or R⁶ and R⁸ together represent a bond and R⁷ and R⁹ are as above defined; or \mathbb{R}^6 and \mathbb{R}^8 together represent -0- and \mathbb{R}^7 and \mathbb{R}^9 are both hydrogen; or R⁶ and R⁷ or R⁸ and R⁹ together represent oxo;
- and each R¹¹ is independently H, trifluoromethyl, (C₁₋₆)alkyl, (C₁₋₆)alkenyl, (C₁₋₆) 35 6)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, aminocarbonyl wherein the amino group is

15

25

WO 00/21948 PCT/GB99/03366

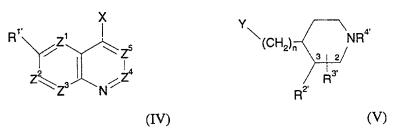
optionally mono- or di-substituted by (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₁₋₆)alkenylcarbonyl, (C₁₋₆)alkenylcarbonyl, (C₁₋₆)alkyl or (C₁₋₆)alkenyl;

- provided that A and B cannot both be selected from NR^{11} , O and $S(O)_X$ and when one of A and B is CO the other is not CO, O or $S(O)_X$.
 - 2. A compound according to claim 1 wherein Z^1 is N and Z^2 - Z^5 are each CH or Z^5 is N and Z^1 - Z^4 are each CH.
- 3. A compound according to claim 1 or 2 wherein R¹ is methoxy, amino(C₃₋₅)alkyloxy, guanidino(C₃₋₅)alkyloxy or fluoro, most preferably methoxy.
 - 4. A compound according to any preceding claim wherein R^3 is in the 3-position and is aminocarbonyl(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl or 1,2-dihydroxy(C_{2-6})alkyl optionally substituted on the hydroxy group(s).
 - 5. A compound according to any preceding claim wherein AB is NHCO, NHCOCH₂ or CH₂CH(OH)CH₂.
- 20 6. A compound according to any preceding claim wherein R^4 is (C_{5-10}) alkyl, unsubstituted phenyl (C_{2-3}) alkyl or unsubstituted phenyl (C_{3-4}) alkenyl.
 - 7. A compound according to claim 1 selected from: [3R, 4S]-1-Heptyl-4-[N-methyl-N-(6-methoxy-quinazolin-4-yl)-2-aminoethyl]-3-ethenylpiperidine;
 - [3R, 4S]-1-Heptyl-4-[2-(6-methoxyquinazolin-4-oxy)ethyl]-3-ethenylpiperidine; 1-Heptyl-4-(6-methoxy-1,5-naphthyridin-4-yl)aminocarbonyl piperidine; [3R, 4S]-1-Heptyl-3-ethenyl-4-N-(6-methoxy-1,5-naphthyridin-4-yl)-piperidineacetamide;
- 30 [3R,4S]-1-Heptyl-3-ethenyl-4-[2-(R,S)-hydroxy-3-(6-methoxy-1,5-naphthyridin-4-yl)propyl]piperidine; [3R,4S]-1-Heptyl-4-N-(6-methoxy-1,5-naphthyridin-4-yl)-3,4-piperidinediacetamide; [3R,4S]-1-Heptyl-4-N-(6-methoxy-1,5-naphthyridin-4-yl)-3-(1-(R,S),2-dihydroxyethyl)piperidineacetamide;
- 35 [3R, 4S]-1-Heptyl-3-ethenyl-4-N-(6-methoxy-cinnolin-4-yl)-piperidineacetamide, [or a pharmaceutically acceptable derivative of any of the foregoing compounds.

8. A process for preparing compounds of formula (I), or a pharmaceutically acceptable derivative thereof according to claim 1, which process comprises:

(a) reacting a compound of formula (IV) with a compound of formula (V):

5



wherein Z^1 , Z^2 , Z^3 , Z^4 and Z^5 , m, n, R^1 , R^2 , R^3 and R^4 are as defined in formula (I), and X and Y may be the following combinations:

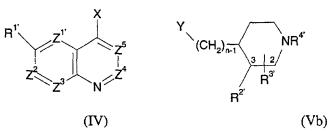
- 10 (i) X is M and Y is CH₂CO₂R^x
 - (ii) X is CO_2R^y and Y is $CH_2CO_2R^x$
 - (iii) one of X and Y is CH=SPh2 and the other is CHO
 - (iv) X is CH3 and Y is CHO
 - (v) X is CH₃ and Y is CO_2R^X
- 15 (vi) X is CH₂CO₂Ry and Y is CO₂R^x
 - (vii) X is CH=PRZ3 and Y is CHO
 - (viii) X is CHO and Y is CH=PRZ3
 - (ix) X is halogen and Y is CH=CH₂
 - (x) one of X and Y is COW and the other is NHR¹¹ or NCO
- 20 (xi) one of X and Y is $(CH_2)_p$ -V and the other is $(CH_2)_qNHR^{11}$, $(CH_2)_qOH$, $(CH_2)_qSH$ or $(CH_2)_qSCOR^x$ where p+q=1
 - (xii) one of X and Y is CHO and the other is NHR11'
 - (xiii) one of X and Y is OH and the other is -CH=N2
- 25 in which V and W are leaving groups, R^X and R^Y are (C_{1-6}) alkyl and R^Z is aryl or (C_{1-6}) alkyl;

or

(b) reacting a compound of formula (IV) with a compound of formula (Vb):

30

10



wherein Z^1 , Z^2 , Z^3 , Z^4 and Z^5 , m, n, R^1 , R^2 , R^3 and R^4 are as defined in formula (I), X is CH_2NHR^{11} ' and Y is CHO or COW or X is CH_2OH and Y is $-CH=N_2$;

- in which R¹¹', R¹', R²', R³' and R⁴' are R¹¹, R¹, R², R³ and R⁴ or groups convertible thereto, and thereafter optionally or as necessary converting R¹¹', R¹', R²', R³' and R⁴' to R¹¹', R¹, R², R³ and R⁴, converting A-B to other A-B, interconverting R¹¹, R¹, R², R³ and/or R⁴ and forming a pharmaceutically acceptable derivative thereof.
 - 9. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof according to claim 1, and a pharmaceutically acceptable carrier.
- 10. A method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment of an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof according to claim 1.
- 20 11. The use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof according to claim 1 in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.
- 12. A pharmaceutical composition for use in the treatment of bacterial infections in mammals comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof according to claim 1, and a pharmaceutically acceptable carrier.